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Antiviral therapy for Ramsay Hunt syndrome (herpes zoster oticus with facial palsy) in adults (Review)

Uscategui T, Doree C, Chamberlain IJ, Burton MJ

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[Intervention Review]

Antiviral therapy for Ramsay Hunt syndrome (herpes zoster oticus with facial palsy) in adults

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ABSTRACT

Background

Herpes zoster oticus (HZO) is a viral infection of the ear and when associated with acute facial paralysis is known as Ramsay Hunt syndrome. Antiviral agents are the standard first-line treatment for herpes zoster infections at other body sites and are thought to reduce or minimise nerve damage, thereby improving outcomes. It has been suggested that these agents improve the chance of facial weakness improving or resolving completely in patients with Ramsay Hunt syndrome.

Objectives

To determine the effectiveness of antiviral agents in the treatment of adult patients with Ramsay Hunt syndrome (HZO with facial palsy).

Search methods

We searched the Cochrane ENT Disorders Group Trials Register, the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library, current issue), Medline (1950 - 2007), PubMed 2007 - 2008, EMBASE (1974 onwards) and other relevant databases. The date of the most recent search was June 2008.

Selection criteria

Two authors scrutinized all possible citations to identify randomised controlled trials in which antiviral agents alone or in combination with other therapies (using different routes of administration and dosage schemes) were given as treatment for Ramsay Hunt syndrome. We contacted an author for further information.

Data collection and analysis

Two reviewers independently assessed eligibility and trial quality.

Main results

Only one randomised, controlled trial was identified and included. It was of low quality and included only 15 participants. In this 1992 trial, intravenous acyclovir and corticosteroids were compared with corticosteroids alone. Our analysis found no statistically significant difference between the two groups.

Authors' conclusions

We found no evidence that anti-viral agents have a beneficial effect on outcomes in Ramsay Hunt syndrome, despite their widespread use in this condition. The use of these drugs in patients with herpes zoster infections in other parts of the body might suggest that they

have a role in herpes zoster oticus. As usual, the absence of positive evidence of benefit (or, in this case, the 'negative' result of one small, statistically under-powered study) does not necessarily indicate that antivirals are ineffective. However, these drugs are associated with a number of adverse effects and this must be taken into consideration when undertaking the requisite risk-benefit analysis before instigating treatment.

PLAIN LANGUAGE SUMMARY

Uncertainty about usefulness of antiviral drugs in Ramsay Hunt syndrome

It seems logical that antiviral drugs might help patients with a herpes virus infection of the ear producing facial weakness (a condition known as 'Ramsay Hunt syndrome'). These drugs often help similar viral infections elsewhere in the body. However, trials that might address this issue have not been done and there is therefore some uncertainty about their usefulness. Since patients can experience side-effects when taking these drugs, the risks of these have to be balanced with the unknown prospect of benefit when considering whether to use them in Ramsay Hunt syndrome.

BACKGROUND

Definition, prevalence and aetiology

Herpes zoster oticus is a viral infection of the inner, middle and external ear characterised by herpetic blisters (small vesicles) of the skin of the external canal, pinna and/or the oral mucosa and severe otalgia (ear pain). These symptoms can be accompanied by one or more of the following: vestibulocochlear dysfunction (e.g. vertigo, hearing loss, hyperacusis, tinnitus), taste impairment, dry mouth and eyes.

When herpes zoster oticus is associated with acute peripheral facial paralysis the condition is known as Ramsay Hunt syndrome type 2 (Ramsay Hunt 1907). Although the terms 'herpes zoster oticus' and 'Ramsay Hunt syndrome' are frequently used interchangeably in the literature, this review will focus only on Ramsay Hunt syndrome and will include trials with participants suffering from herpes zoster oticus with accompanying facial weakness.

The incidence of Ramsay Hunt syndrome is about five cases per 100,000 of the US population annually, with a significantly increased incidence in patients older than 60 years (Murakami 1997). The condition is considered to be both less frequent and less severe in children (Hato 2000; Sweeney 2001), but reports of children are limited in the literature and the clinical features and prognosis of paediatric Ramsay Hunt syndrome remain unclear. Vaccination against chickenpox (both in childhood and in later life) may prevent or reduce its occurrence (Guess 1985; Hato 2000; Oxman 1995).

Ramsay Hunt syndrome is caused by the reactivation of latent varicella-zoster virus in the geniculate ganglion (the sensory ganglion of the facial nerve) which affects the seventh and eighth cranial nerves. This is due to the close proximity of the facial nerve (cranial nerve VII) and the vestibulocochlear nerve (cranial nerve VIII) (Sweeney 2001). The subsequent dysfunction of cranial nerves VII and VIII is thought to be caused primarily by varicella-zoster virus neuritis and to a lesser extent by inflammatory oedema. Maximal facial paralysis is generally seen within one week. Although less common than Bell's palsy (i.e. idiopathic facial palsy), Ramsay Hunt syndrome generally causes more severe dysfunction and has a poorer prognosis for facial nerve recovery (Uri 2003). There are currently three published Cochrane reviews and one published Cochrane protocol covering interventions for Bell's palsy (Allen 2004; He 2007; Salinas 2004; Teixeira 2006).

History, examination and diagnosis

Diagnosis is primarily clinical and is based on the presentation of a combination of severe ear pain, small vesicles on the pinna or oral mucosa and facial palsy. When patients present with acute facial weakness a high index of suspicion is required in order to recognise the condition, deliver prompt treatment and obtain the best possible outcome. Although the appearance of vesicles usually precedes or presents simultaneously with facial paralysis, it may be delayed until after facial weakness is clinically evident, thus making the condition initially indistinguishable from Bell's palsy. Symptoms and signs of vestibulocochlear dysfunction are not always present, but can include hearing loss, tinnitus, vertigo, nystagmus, nausea and vomiting.

The clinical picture remains the cornerstone of diagnosis, as serum titres of varicella-zoster virus antibodies are only useful when comparing the acute and convalescent stages of the condition (Dickins 1988). The use of a polymerase chain reaction (PCR) to detect varicella-zoster virus from skin of the affected area of the ear may help to distinguish between patients with Bell's palsy and those with Ramsay Hunt syndrome in the very early stages (Murakami 1998).

The *early* diagnosis of Ramsay Hunt syndrome is always said to be extremely important. In the treatment of herpes infections in general, antiviral therapy is most effective when given within the first 72 hours of the onset of symptoms (Dworkin 2007). If diagnosis is made and antiviral treatment commenced within this timeframe, the facial palsy recovery rate has been reported in non-randomised studies to be as high as 75% (Dickins 1988; Murakami 1997). Significant factors for increased risk of poor prognosis are said to include: the absence of demonstrable nerve excitability, complete paralysis and being aged over 50 years at presentation (Sweeney 2001). In contrast, the prognosis for associated sensorineural hearing loss is excellent, and only around 5% of patients will have residual hearing impairment (Kaberos 2002; Murakami 1997). Other potentially chronic sequelae are post-herpetic neuralgia, tinnitus and vestibular dysfunction (Dworkin 2007).

Management options

The standard first-line treatment for herpes zoster infections at sites in the body other than the ear is the anti-viral agent acyclovir, which is given either intravenously or orally. Other antiviral agents that may be prescribed include valacyclovir (Beutner 1996), famcyclovir (Tyring 1995) or brivudin (Dworkin 2007).

Antiviral therapy is only effective against virus *replication* in herpes zoster infections - that is, it can prevent further proliferation and spread of the varicella-zoster virus but cannot eradicate the viruses. Oral antiviral treatment has been evaluated in the treatment of herpes zoster infections in other parts of the body and has been shown by two meta-analyses (of four and five randomised controlled trials respectively) to lessen the severity of herpes zoster infection in immunocompetent adults. It reduces the duration of viral shedding and new lesion formation, thereby accelerating rash healing and reducing the duration of pain (Jackson 1997; Wood 1996).

It is generally held that the use of oral antivirals is limited to a period of 7 to 10 days and needs to be started within 72 hours of the onset of a rash. They are generally very well tolerated if administered at standard doses (acyclovir: 800 mg five times/day for 7 to 10 days; famcyclovir: 500 mg three times/day for seven days; valacyclovir: 1000 mg three times/day for seven days) and providing patients are kept well hydrated (Dworkin 2007; Goodman 2006; Kinishi 2001; Lampee 1986). The most common side effects are nausea (and occasionally vomiting) and headache, which occur in 10% to 20% of cases. Other possible side effects from prolonged use include renal impairment, diarrhoea, dizziness, fatigue, skin rash, anorexia, leg pain, sore throat and hair loss (Bean 1982; Dickins 1988). Any allergic reaction to antiviral medications is a contraindication to their use (Peterslund 1981).

Oral brivudin appears to have a higher potency against varicella-zoster virus than the oral regimes of acyclovir, valacyclovir and famcyclovir. It also has a simpler regime (once a day) and no nephrotoxic effects (Dworkin 2007; Gross 2003). However, antivirals cannot prevent either the acute or chronic pain produced by the

infection and experienced by about 20% of patients over 50 years of age, and therefore supplementary therapies, most frequently adjuvant corticosteroids, are often prescribed. The rationale for their use is to reduce nerve inflammation and associated pain.

Although antivirals have become standard therapy for Ramsay Hunt syndrome in Europe and the US in recent years, and a number of primary studies assessing their effectiveness have been published, we found no systematic review of randomised studies addressing this question. Therefore, this systematic review aims to evaluate the effects of antiviral therapy on outcomes in patients with Ramsay Hunt syndrome.

OBJECTIVES

To determine the effectiveness of antiviral agents in the treatment of adult patients with Ramsay Hunt syndrome (herpes zoster oticus with facial palsy).

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled trials in which antiviral agents are used in the treatment of Ramsay Hunt syndrome.

Types of participants

Adults (≥18 years) with a clinical diagnosis of Ramsay Hunt syndrome treated within seven days of onset. Studies of adults and children were to be included if adult data could be extracted separately. Paediatric patients (<18 years) were excluded on the grounds that specific immunity against the virus and its reactivation is generally considered to be significantly stronger in children than in adults, resulting in milder clinical manifestations and better outcomes in this patient group (Hato 2000). It was expected that trials will have excluded immunocompromised adults.

Types of interventions

Trials using any antiviral agent irrespective of the route of administration (oral, enteral or parenteral) and the length of treatment.

Types of outcome measures

Primary outcomes

Proportion of patients with complete recovery of facial palsy six months after initial diagnosis. Complete recovery is defined as equivalent to Grade II or better on the House Brackmann scale (Table 1; House 1985). Studies using equivalent recognised and/or validated grading scales will also be included.

Secondary outcomes

1. Proportion of patients with motor synkinesis (involuntary facial movement, e.g. facial spasm) or autonomic dysfunction (e.g. crocodile tears) at six months.
2. Proportion of patients with persistent vestibulocochlear symptoms, e.g. symptoms of balance impairment, sensorineural hearing loss (measured using pure tone audiometry) or tinnitus at six months.
3. Any adverse effects.

Search methods for identification of studies

We searched the Cochrane ENT Group Trials Register, the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library*, current issue), Medline (1950 - 2007), PubMed 2007 - 2008, and EMBASE (1974 onwards). The date of the most recent search was June 2008. The following databases were also searched: CINAHL (1982 onwards), LILACS, KoreaMed, IndMed, PakMediNet, the UK Clinical Research Network Portfolio Database (UKCRN), the World Health Organization International Clinical Trials Registry Platform (ICTRP), Google Scholar, NLH ENT & Audiology Specialist Library and the *meta*Register of Controlled Trials (*m*RCT).

The Cochrane Central Register of Controlled Trials (CENTRAL) was searched using the search terms listed in Appendix 1. These terms were combined with the first two sections of the highly sensitive search strategy designed by The Cochrane Collaboration for identifying randomised controlled trials and controlled clinical trials in the PubMed and EMBASE databases. Strategies for all other databases were modelled on the CENTRAL version. The strategies were also combined with a search filter designed to retrieve cost-effectiveness studies in MEDLINE and EMBASE, and the NHS Economic Evaluation Database (in *The Cochrane Library*) was also searched for relevant studies.

References of retrieved articles from electronic searches were searched and a search for existing meta-analyses and non-Cochrane systematic reviews was performed. Reference lists were scanned for additional trials. No language, publication year or publication status restrictions were placed on searching.

Data collection and analysis

Study selection

Randomised controlled trials including adults receiving antiviral therapy for Ramsay Hunt syndrome were selected. There were no language exclusions.

Data extraction

Data from studies were independently extracted by two groups of authors using standardised data forms. Data were extracted so as to allow an intention-to-treat analysis. Where data were missing, the authors wrote to the authors of the study requesting the missing data.

Quality assessment

The quality of the trials was assessed and graded independently by two authors according to the criteria described in The Cochrane Handbook 4.2.6 (Higgins 2006). Gradings were compared and any inconsistencies between the authors in the interpretation of inclusion criteria and their significance to the selected study were discussed and resolved.

The selected study was assessed for the following characteristics:

1. The adequacy of the randomisation process (possible selection bias). Adequate randomisation includes any one of the following methods: computer generated or table of random numbers, drawing of lots, coin-toss, shuffling cards or throw of a dice. Inadequate methods of randomisation include the following: case record number, date of birth or alternate numbers.

2. The adequacy of the allocation concealment (possible selection bias). Adequate methods of allocation concealment include either central randomisation (i.e. separate to other aspects of trial administration) or sequentially numbered sealed opaque envelopes. Inadequate concealment means an open allocation sequence in which either participants or trialists were able to foresee the upcoming assignment.
3. The blinding of outcome assessors (i.e. whether the persons assessing the outcome of care were aware of which treatment the participant had received - possible performance bias).
4. The extent and handling of losses to follow up (possible attrition bias). Adequate handling of losses to follow up involves a clear description and explanation being given of any significant difference between the losses of the intervention groups. An unacceptable loss in any one intervention group was considered to be loss greater than 20%.

Study gradings A, B or C were employed for overall quality as follows.

A: Minimisation of bias in all four categories above: i.e. adequate randomisation, few losses to follow up and intention-to-treat analysis, blinding of outcome assessors, high quality outcome assessment;
B: Each of the criteria in A partially met;
C: One or more of the criteria in A not met.

Data analysis

Owing to there being only one included study, a meta-analysis was not possible. If further eligible studies are identified in future updates, we intend to perform meta-analysis if appropriate. Our primary measure of treatment effect is dichotomous (presence or otherwise of complete recovery of facial palsy at six months) and the risk ratio (RR) of this will be determined for each included study. Data will be analysed by intention-to -treat (ITT). Sensitivity analyses will be performed in which we will assume that 1) all missing participants failed to recover and 2) all missing participants recovered completely. The Mantel-Haenszel fixed-effect method will be used for the meta-analysis and the I^2 statistic used to investigate heterogeneity.

RESULTS

Description of studies

Of the 195 abstracts retrieved from our search, we discarded all but three after perusal of the abstracts. Several of these studies evaluated antivirals in the management of generalised (non-otological) herpes zoster infections. Two of the three possible studies were subsequently excluded as they were not randomised controlled trials (Kinishi 2000; Uri 2003); see Table of Excluded Studies.

One trial (Ramos Macias 1992) met our inclusion criteria. This study enrolled 15 patients with Ramsay Hunt syndrome with ages ranging from 21 to 91 years. No details are given about the timing of the onset, diagnosis or enrolment in the study. Details of the randomisation and allocation concealment are not stated in the original paper. This information was obtained from the principal author who confirmed that the randomisation process and the allocation were computer generated.

Seven patients had 'complete axonotmesis' and eight had 'incomplete' palsies. This is problematic because no information is given about the distribution of these two categories between the treatment and control groups. For example, we cannot be certain that all the patients with the incomplete palsies were not in the treatment group and the more severely affected patients in the control group.

All participants received intravenous corticosteroids (methylprednisolone 20 mg/8 hours for 10 days). Seven participants only received this treatment (control group) whilst eight (the treatment group) received in addition intravenous acyclovir (10 mg/kg/8h for 10 days). It is not clear whether the participants or study personnel (and in particular those assessing outcomes) were blinded to the allocation.

Risk of bias in included studies

We classified this study as grade C because of the uncertainty about blinding. The possibility of an uneven distribution of complete and incomplete palsies between the two groups is another potential source of bias and we conclude overall that this is a low quality study.

Effects of interventions

It is not clear from the published data (Ramos Macias 1992) at what time point the reported outcomes were assessed. One patient in the treatment group (N = 8) abandoned their treatment due to a generalised rash. The remainder achieved the following levels on the House-Brackmann scale:

Grade I : 3

Grade II : 2

Grade III: 1

Grade IV : 1

The proportion of patients with Grade II or I was 5/8 (63%). Intention to treat principles were followed and the patient who discontinued treatment was included in the denominator.

The results in the control group (N = 7) were:

Grade I : 1

Grade II : 2

Grade III : 3

Grade IV : 0

Grade V : 1

The proportion of patients with Grade II or I was 3/7 (43%).

There is no statistically significant difference between the two groups (Analysis 1.1). No information is available about any other outcome measures. Only one adverse event (as mentioned above) was reported.

DISCUSSION

We found no evidence that anti-viral agents have a beneficial effect on outcomes in Ramsay Hunt syndrome, despite their widespread use in this condition. The use of these drugs in patients with herpes zoster infections in other parts of the body might suggest that they have a role in Ramsay Hunt syndrome. As usual, the absence of positive evidence of benefit (or, in this case, the 'negative' result of one small, statistically under-powered, study) does not necessarily indicate that antivirals are ineffective. However, these drugs are associated with a number of adverse effects and this must be taken into consideration when undertaking the requisite risk-benefit analysis before instigating treatment.

AUTHORS' CONCLUSIONS

Implications for practice

Anti-viral agents may, or may not, be effective in patients with Ramsay Hunt syndrome. On the basis of fundamental patho-physiological principles it would seem reasonable to use them. However, these agents are associated with a number of side effects and adverse events which must be considered before they are prescribed.

Implications for research

High quality, appropriately powered randomised controlled trials are required to evaluate the effect of antiviral agents in patients with Ramsay Hunt syndrome (herpes zoster oticus with accompanying facial weakness). Such studies should include:

Participants - with Ramsay Hunt syndrome within 7 days of onset. The degree of facial weakness (complete/incomplete, and the degree of the latter) should be stated for all participants and treatment and control groups should be balanced.

Interventions - oral antiviral agents with or without concomitant administration of steroids (see our companion review Uscategui 2008)

Outcomes - improvement in facial movement (specifically proportion of participants with complete/near complete recovery), presence of motor synkinesis or autonomic dysfunction at six months. In addition presence of vestibulocochlear symptoms, e.g. balance impairment, sensorineural hearing loss or tinnitus. Presence of any adverse effects.

ACKNOWLEDGEMENTS

We acknowledge the assistance of Professor A Ramos Macias in providing additional information about his study

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Ramos Macias 1992

Methods	
Participants	15 patients with Ramsay Hunt syndrome aged between 21 and 91. No indication of duration of symptoms. At outset 7 had "complete axonotmesis" (assumed to be = complete palsy) and 8 "incomplete forms (..neuropraxia)" but distribution between treatment and control groups not given.
Interventions	Control group: i.v. methylprednisolone 20mg/8 hours for 10 days followed by "gradually decreasing dose of oral prednisolone during 5 or 10 days" (N=7) Treatment group: i.v. methylprednisolone 20 mg/8 hours for 10 days PLUS i.v. acyclovir 10 mg/kg/8h for 10 days (N=8) followed by "gradually decreasing dose of oral prednisolone during 5 or 10 days"
Outcomes	House-Brackmann grading of facial movement at an unstated time point after completion of treatment.
Notes	

Ramos Macias 1992 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Prinicipal author stated that computer generated allocation was used
Allocation concealment?	Low risk	Prinicipal author stated that allocation was concealed
Blinding? All outcomes	Unclear risk	No mention of study personnel or participants being blind to treatment group
Incomplete outcome data addressed? All outcomes	Low risk	All participants accounted for, one 'drop out' recorded but included by us in analysis
Free of other bias?	Unclear risk	Possible uneven distribution of complete and incomplete paralysis at start of study between the two treatment groups

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Kinishi 2000	ALLOCATION: Non-randomised study
Uri 2003	ALLOCATION: Non-randomised study; no comparator group

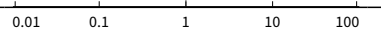
DATA AND ANALYSES

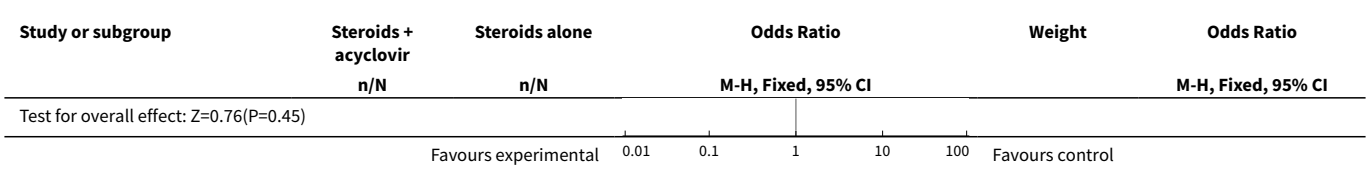
Comparison 1. Steroids + acyclovir versus steroids alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 House Brackmann Grades I & II	1	15	Odds Ratio (M-H, Fixed, 95% CI)	2.22 [0.28, 17.63]

Analysis 1.1. Comparison 1 Steroids + acyclovir versus steroids alone, Outcome 1 House Brackmann Grades I & II.

Study or subgroup	Steroids + acyclovir n/N	Steroids alone n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Ramos Macias 1992	5/8	3/7		100%	2.22[0.28,17.63]
Total (95% CI)	**8**	**7**		**100%**	**2.22[0.28,17.63]**
Total events: 5 (Steroids + acyclovir), 3 (Steroids alone)					
Heterogeneity: Not applicable					





ADDITIONAL TABLES

Table 1. House Brackmann classification

Grade	Description	Measurement	Function %	Estimated Function %
I	Normal	8/8	100	100
II	Slight	7/8	76-99	80
III	Moderate	5/8-6/8	51-75	60
IV	Moderately Severe	3/8-4/8	26-50	20
V	Severe	1/8-2/8	1-25	20
VI	Total	0/8	0	0

APPENDICES

Appendix 1. Search strategy

#1 HERPES ZOSTER OTICUS single term (MeSH)
#2 FACIAL PARALYSIS single term (MeSH)
#3 HERPES ZOSTER single term (MeSH)
#4 #2 AND #3
#5 (ramsay OR ramsey) NEXT hunt*
#6 (hunt* NEXT (disease OR syndrome OR neuralgia)) NOT (tolosa OR tolusa OR hunter* OR hunting*)
#7 (zoster* OR herpe* OR herpesvirus*) AND (otic* OR auric* OR cephalic* OR pinna* OR otologic* OR acoustic OR auditory OR ear* OR geniculate OR cochleovestibular OR vestibulocochlear OR facial NEAR weakness OR facial NEAR palsy OR facial NEAR paralys*)
#8 #1 OR #4 OR #5 OR #6 OR #7

WHAT'S NEW

Date	Event	Description
6 June 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

All authors were involved in formulating the protocol.

CD undertook the searches and with TU screened the identified citations.

TU, IJC & MJB extracted data

CD, TU, IJC and MJB wrote the paper

DECLARATIONS OF INTEREST

None known.

INDEX TERMS

Medical Subject Headings (MeSH)

Antiviral Agents [*therapeutic use]; Facial Paralysis [*drug therapy]; Herpes Zoster Oticus [*drug therapy]; Randomized Controlled Trials as Topic; Syndrome

MeSH check words

Adult; Humans